

REMARKS

Upon entry of the amendment, claims 11, 13-16, 20-22, and 42-59 are pending in the application. Support for the amendments to claim 11 can be found on p. 13, lines 21-30 and p. 26, line 5 through p. 28, line 12. Support for the amendment to claims 13 and 14 can be found on p. 14, line 18 through p. 15, line 8, and in Example 1, p. 30, line 4.

I. 35 U.S.C. 112, First Paragraph Rejection – Written Description

Reconsideration is requested of the rejection of claims 11, 13-16, and 20-22 under 35 U.S.C. §112, first paragraph on the asserted basis that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed.

"Compliance with the written description requirement is essentially a fact-based inquiry that will **'necessarily vary** depending on the **nature of the invention** claimed.'" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002)(citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991))(emphasis added). The standard is whether the description allows persons of ordinary skill in the art **to recognize** that the inventor had possession of the claimed invention at the time of filing. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (emphasis added); *see also, Vas-Cath*, 935 F.2d at 1557.

According to the Office, in "Table 1 applicant identifies over 180 dyes that were evaluated. Table 2 lists 40 anionic dyes that were selected for further study. Upon review of Table 2, only four dyes, Acid Red 4, Acid Red 1, Amaranth, and Acid Violet 5 were found to be suitable." Not only is this assertion inconsistent with what is stated in Example 1, it is expressly refuted by the declaration of Brian Ward which accompanied applicant's Amendment B. Nowhere is it stated or even suggested that 140 of the 180 "red" dyes identified in Table 1 were unsuitable. Rather, **only** 40 of these were selected for evaluation. Of the 40 selected for evaluation, seventeen were removed

from consideration **solely on the basis of aesthetics** (they were considered to be too yellow/orange or purple) and 3 were eliminated for reasons related to solubility. Of the 23 remaining, 6 (i.e., **more than 25%**) were found to be relatively inert in the PCR reaction; the other 17 were found to yield undesirably colored pellets or eluants or significantly inhibited the PCR reaction.¹

In view of this record, a person of ordinary skill would have recognized that applicants were in possession of much more than the acid red 1/acid violet 5 combination selected for the "REDTaq™" composition exemplified in Example 1. More specifically, a person of ordinary skill would have recognized that had applicants not been arbitrarily seeking a particular shade of red, a number of dyes could have readily been substituted for acid red 1 and acid violet 5.

With respect to optical density, it must be recognized that optical density is merely a measure of the transmittance of a composition. As applied in this instance, optical density is merely a surrogate measure of the concentration of the tracer dye in the composition: an increase in tracer dye concentration leads to an increase in optical density and *vice versa*.

According to their specification, applicants prefer compositions having an optical density of between about 5 and about 500.² In their Example 1, applicants exemplify the preparation of a composition having an optical density near the middles of this range, i.e., of 300, using 80% acid red 1 and 20% acid violet 5.³ Since optical density is a measure of concentration, applicants could have prepared a composition having a lesser optical density simply by incorporating less of the dye in the composition or, alternatively, could have prepared a composition having a greater optical density simply by incorporating more of the dye in the composition. In view of this disclosure, a person of ordinary skill clearly would have understood that persons of ordinary skill were in possession of compositions having an optical density greater than 5.

¹Applicants' specification at page 27, lines 12-15.

²Specification at page 13, lines 27-31.

³Specification at page 30, lines 1-6.

The Office asserts that the specification fails to demonstrate a composition with a density of "at least about 1.01 g/cm³" or "at least about 1.1 g/cm³." Specifically, it is the Office's position that the stated densities encompass values ranging to infinity, and that the specification does not provide support for such.

As described in Applicant's specification, to assist in the addition of reaction mixture to the analytical process, the density of the reaction mixture should be at least about 0.01 g/cm³ greater than the density of the liquid phase of the analytical process. Applicants further describe the use of sugars, glycerol or betaine for this purpose, with glycerol being preferred. A particularly preferred solute for increasing the viscosity is glycerol, which at a concentration of 50% in water has a density of about 1.14 gm/cm³.⁴ In view of this disclosure, a person of ordinary skill would have understood from applicants' disclosure that they considered their invention to include compositions having a range of densities, that applicants had provided persons of ordinary skill with the means to control density (by including an appropriate density increasing solute), that they had exemplified a composition having a viscosity of 1.14 gm/cm³, and that there would be no benefit derived from going to unusually great densities. As such, a person of ordinary skill would have understood applicants to be in possession of compositions having a density of at least 1.01 gm/cm³.

With respect to claims 20-22, a composition comprising Taq polymerase, acid red 1, and acid violet 5 with the claimed optical density and density is demonstrated in Example 1. Specifically, Example 1 sets forth a composition comprising 1 u/μl Taq polymerase in Taq storage buffer (consisting of 20 mM Tris-HCl, pH 8.0, 100 mM KCl, 0.1 mM EDTA, 1 mM DTT, 0.5% Tween 20, 0.5% Igepal® CA-630, 50% glycerol in water) with the magnesium formulation of dye at a total absorbance of 300. The dye composition was 80% acid red 1, 20% acid violet 5 (100%= absorbance of acid red 1 at λ_{max} + absorbance of acid violet 5 at λ_{max} , absorbance of acid red 1=240, acid violet 5=60). This embodiment of the claimed composition demonstrates applicants were in possession of the invention defined by each of claims 20-22.

⁴ Specification, p. 15, lines 4-6.

In summary, based upon the general description within the specification, in addition to the specific example contained therein and the knowledge and skill of those in the art, one of skill in the art would recognize that Applicants were in possession of the claimed invention at the time of filing the application.

The Office maintains its position that Applicants have failed to demonstrate the genus of thermostable DNA polymerases and anionic tracer dyes that comprise the claimed composition, and have, therefore, failed to demonstrate the claimed genus. Applicants maintain that it would have been understood or recognized by one of skill in the art by Applicants' disclosure of Taq polymerase as the DNA polymerase of the claimed composition that Applicants were in possession of the broader genus of compositions wherein the composition comprised any thermostable DNA polymerase as its polymerase component. The standard, as properly argued by Applicants, is whether the description allows persons of ordinary skill in the art **to recognize** that the inventor had possession of the claimed invention at the time of filing. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996)(emphasis added); *see also, Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1557 (Fed. Cir. 1991)).

Furthermore, the Office asserts that Brian W. Ward stated in his declaration⁵ that one of skill in the art would assume that possession of one thermostable polymerase would constitute possession of all thermostable polymerases,⁶ and that the claims are not drawn to a DNA polymerase *per se*, but to a composition that comprises the same.⁷ While Applicants agree that the claimed invention is not drawn to a DNA polymerase *per se*, but to a composition that comprises the same, Applicants disagree with the Office's interpretation of Dr. Ward's statement. Specifically, Dr. Ward stated

⁵ Declaration of Brian W. Ward, submitted as Exhibit A with Applicants' response dated July 29, 2002.

⁶ Office Action of September 11, 2002, Paper No. 17, ¶ 10.

⁷ Office Action of September 11, 2002, Paper No. 17, ¶ 11.

8. . . . Therefore, as one of ordinary skill in the art, the disclosure and use of Taq polymerase in Example 1 of the present application would be sufficiently descriptive to confer to me and others that the Applicants of the present invention were in possession not only of the particular embodiment disclosed above, but of all such embodiments comprising a DNA polymerase, and more particularly a thermostable polymerase, and a tracer dye, and more particularly an anionic dye. Specifically, because of the high knowledge and skill in the art regarding the structure, function, and use of polymerases, and in particular thermostable polymerases, one would be well aware of the fact that the Applicants were in possession of **all of the embodiments of the invention as claimed** at the time of filing the present application.

...

19. . . . [T]his knowledge [of the common structure, function, and use of thermostable DNA polymerases] and skill, combined with the disclosure of Example 1,4 would be sufficient to convey to those of even moderate skill in the art that Applicants were in possession of not only a **composition** comprising Taq polymerase as the polymerase component of the composition, but of a **composition** comprising any DNA polymerase.

(emphasis added).⁸ It is his opinion therefore, that all other requirements being demonstrated, one of skill in the art would believe Applicants were in possession of a composition comprising, *inter alia*, any DNA polymerase and more particularly, any thermostable DNA polymerase.

Furthermore, Applicants have demonstrated dyes of a red color that meet the limitations of the claimed invention. The demonstration of these particular red dyes meeting the limitations of the claims are sufficient to convey to one of skill in the art that Applicants were in possession of all such colored dyes that meet the same limitations.

Specifically, Applicants were in possession of dyes of other colors. Applicants screened numerous dyes based upon various factors, some of which were based upon performance characteristics, and others that were not. Of the factors that were not based upon performance was a determination of the color of the dyes which Applicants

⁸ Ward Declaration, ¶¶ 8 and 19, originally submitted 2002.

possessed. Applicants opted not to **specifically** test dyes of any color other than red. The decision to test these dyes was not because it was believed that they were inadequate, but simply because Applicants opted to test red dyes first. There is no reason to believe that dyes of other colors, provided they meet the limitations of being anionic and compatible with the thermostable DNA polymerases, would not also work as well as the red dyes specifically detailed in the Examples.

Specifically, red anionic tracer dyes that do not meet the claim limitations, and that were eliminated for that fact, include those that failed a PCR toxicity test.⁹ This test was used to determine whether an anionic dye is compatible with the thermostable DNA polymerase – *i.e.*, whether the dye would significantly interfere with the enzyme reaction¹⁰ – and therefore, whether the anionic dye meets that limitation of the claims.

Red dyes, therefore, that are not compatible with the claimed invention are not so because of their red color, but because of incompatibility with the thermostable polymerase. One of ordinary skill in the art would clearly understand that dyes of other colors that fail to meet this limitation could not be used in the claimed composition, as they are not compatible with the intended uses of the composition. Just as clear to one of skill in the art is the fact that anionic dyes of colors other than red that are compatible with the thermostable DNA polymerase would also work well in the claimed composition. The limitation of compatibility with a thermostable DNA polymerase having been met, the particular color of the dye is completely innocuous. Applicants specific demonstration of the compositions using red anionic dyes is nothing more than a demonstration of a preferred embodiment of the claimed invention, and is so

⁹ Additional tests that were performed include ethanol precipitation, ligase toxicity, and transformation toxicity. See, Specification, p. 26 line 5 through p. 28, line 12.

¹⁰ Specification, p. 12, lines 21-25.

indicated in the specification.¹¹ These points are further elaborated in the Ward Declaration.¹²

It would therefore be clear to one of ordinary skill that, in spite of the fact that Applicants did not particularly demonstrate dyes of other colors in the Examples, Applicants were in possession of the claimed compositions wherein the dye is one other than the four specifically demonstrated in the examples. Indeed, one of skill would understand, especially in light of the specific teachings of the present specification as to how to obtain dyes compatible with a thermostable DNA polymerase, that the color of the dye does not affect the composition, and that Applicants purposeful demonstration of red anionic dyes only is a clear indication of their belief that any color tracer dye meeting the other claim limitations would suffice. Furthermore, one of skill would recognize that Applicants determination of the color of the dyes in their possession, and the decision to specifically test or not test dyes of a particular color as based solely on esthetics, indicates that Applicants were in possession of compositions that comprise these non-tested dyes.

II. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 11, 13-16, and 20-22 under 35 U.S.C. 103(a) as being unpatentable over Köster et al. (U.S. Patent No. 5,928,906) in view of Nardone et al. (U.S. Patent No. 6,117,986).

As amended, claim 11 is directed to a composition comprising a thermostable DNA polymerase and an anionic dye, the composition being substantially free of a nucleic acid polymer template and having an optical density of about 5 to about 500.

Köster et al ("Köster") discloses compositions that comprise a dye and a DNA polymerase. Taq polymerase is disclosed in one particular embodiment. These compositions are used in a sequencing method to detect the presence of specific nucleotide sequences. However, Köster et al. do not disclose the use of an anionic

¹¹ Specification, p. 13, lines 10-14; p. 26, lines 1-3; p.29, lines 20-22.

¹² See, Ward Declaration, ¶¶ 20-27.

tracer dye or the use of Acid Red 1 or Acid Violet 1 in their compositions; instead, they use a variety of other dyes.¹³

Nardone et al. ("Nardone") disclose labeled mononucleotides and methods of producing the same. Specifically, Nardone et al. disclose compositions comprising mononucleotide precursors, and in particular pyrimidines, covalently coupled to a quencher molecule. This quencher nucleotide is incorporated into a larger labeling oligonucleotide having a fluorescent dye at the 5' end of the oligonucleotide and used to detect specific nucleotide sequences. Nardone et al. further disclose that the quencher molecule can be either acid red 1 or acid violet 5. Significantly, however, Nardone et al. do not disclose the use of acid red 1, acid violet 5, or combinations thereof as a detectible anionic tracer dyes. Instead, they use it as a quencher for another dye, a fluorescent dye, which serves as the tracer.

In combination, Köster et al. and Nardone et al. fail to render the claimed invention obvious. Köster et al. employ tracer dyes, but not one fitting the requirements of claim 11. In addition, Köster et al. disclose nothing of significance concerning their dyes. Nardone et al. disclose the use of acid red 1 and acid violet 5, but only as a **quencher** for a fluorescent dye. As such, what would have motivated a person of ordinary skill to substitute Nardone et al.'s quencher for Köster et al.'s dye? The Office provides no reason and none is apparent on this record. Rather, it appears the Office engaged in an impermissible hindsight reconstruction of the claimed invention. In the absence of a motivation to combine the references, a *prima facie* case of obviousness has not been established.¹⁴

Furthermore, and in any event, the two references fail to teach or suggest each of the requirements of claim 11. Neither Köster et al. or Nardone et al. disclose or suggest a composition having an optical density of at least 5 at a visible wavelength of maximal tracer absorbance.

¹³See, Example 1 of Köster et al.

¹⁴ MPEP §2142.

Claims 13-16 and 20-22 depend, either directly or indirectly, from claim 11 and are patentable over Köster et al. in combination with Nardone et al. for the reasons stated with respect to claim 11 and by reason of the additional requirements which they introduce.



VERSION WITH MARKINGS TO SHOW CHANGES MADE

The Claims have been amended as follows:

11. (twice amended) A composition comprising a thermostable DNA polymerase for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared, and **[an]** a detectible anionic tracer dye compatible with the thermostable DNA polymerase, the composition being substantially free of the nucleic acid polymer template and having an optical density **[greater than]** of about 5 to about 500 at a visible wavelength of maximal tracer absorbance.

13. (twice amended) The composition of claim 11 having a density of **[at least]** about **[1.01 g/cm³]** 0.01 g/cm³ greater than the density of an analytical liquid phase to 0.14 g/cm³ greater than the density of an analytical liquid phase.

14. (twice amended) The composition of claim 11 having a density of **[at least]** about **[1.1 g/cm³]** 1.14 g/cm³.

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CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 11, 13-16, and 20-22 under 35 U.S.C. 112, first paragraph, and 35 U.S.C. 103(a).

A check in the amount of \$410.00 for a two month extension of time is enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "E. Hejlek".

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